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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROYDS, LESLIE A	

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1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,029	CONN ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6,7,10-12 and 14-18* is/are pending in the application.

4a) Of the above claim(s) *6,7,11,12 and 15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,10,14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09 Jan 06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3, 6-7, 10-12 and 14-18 are presented for examination.

Acknowledgement is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/US04/21776, filed July 7, 2004, which claims benefit under 35 U.S.C. 119(e) to U.S. Provisional Patent Application No. 60/486,691, filed July 11, 2003.

Applicant's Information Disclosure Statement (IDS) filed January 9, 2006 (two pages total) has been received and entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08A, the Examiner has considered the cited references.

Applicant's response filed August 13, 2007 to the requirement for restriction/election dated July 11, 2007 has been received and entered into the present application. Pursuant to the requirement for restriction/election dated April 22, 2008, the requirement for restriction/election dated July 11, 2007 was vacated in lieu of the requirement dated April 22, 2008. Applicant's response filed May 13, 2008 to the requirement for restriction/election dated April 22, 2008 has been received and entered into the present application, but was non-compliant pursuant to the notice dated September 24, 2008. Applicant's response filed October 20, 2008 correcting the deficiencies set forth in the notice dated September 24, 2008 has also been received and entered into the present application.

Requirement for Restriction/Election

Applicant's election, **without traverse**, of the invention of Group III (claims 1, 3, 6-7, 10 and 14-18), directed to a method for treating, preventing the progression, ameliorating, controlling or reducing the risk of a movement disorder in a patient in need thereof that comprises administering to the patient a therapeutically effective amount of a mGluR4 receptor positive allosteric modulator or a pharmaceutically acceptable salt thereof, and the election of the species of (i) Parkinson's disease as the movement disorder, (ii) N-phenyl-7-(hydroxylimino)cyclo-propa[b]chromen-1a-carboxamide ("PHCCC") as the

mGluR4 receptor positive allosteric modulator, and (iii) the mGluR4 receptor positive allosteric modulator is not administered in combination with another agent, in the reply filed October 20, 2008 is acknowledged by the Examiner.

Therefore, for the reasons above and those made of record at p.2-10 of the previous Office Action dated April 22, 2008, the requirement remains proper and is hereby made **FINAL**.

Claims 6-7, 11-12 and 15-18 are **withdrawn** from examination pursuant to 37 C.F.R. 1.142(b) as being directed to non-elected subject matter.

The claims corresponding to the elected subject matter are claims 1, 3, 10 and 14 and such claims are herein acted on the merits.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 10 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment, amelioration, control or reduction in the risk of Parkinson's disease using the instantly claimed compound N-phenyl-7-(hydroxylimino)cyclo-propa[b]chromen-1a-carboxamide, does not reasonably provide enablement for preventing or preventing the progression of the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;

2) the breadth of the claims;

3) the predictability or unpredictability of the art;

4) the amount of direction or guidance presented;

5) the presence or absence of working examples;

6) the quantity of experimentation necessary;

7) the state of the prior art; and,

8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

For the purposes of consideration under 35 U.S.C. 112, first paragraph, it is noted that the instant specification defines the term "treating" as used in the claims as also circumscribing the aspect of prevention. Please see p.8, l.14-15 of the instant specification, which states, "As used herein, the term 'treatment' refers both to the treatment and to the prevention or prophylactic therapy of the aforementioned conditions." Accordingly, in view of such a definition provided by Applicant, the claims are understood to also include prevention of Parkinson's disease.

The presently claimed invention is directed to a method for treating, preventing the progression, ameliorating, controlling or reducing the risk of a movement disorder, i.e., in this case, Parkinson's disease, in a patient in need thereof that comprises administering to the patient a therapeutically effective amount of an mGluR4 receptor positive allosteric modulator or a pharmaceutically acceptable salt thereof, i.e., in this case, the compound N-phenyl-7-(hydroxylimino)cyclo-propa[b]chromen-1a-carboxamide.

In particular, one skilled in the art could not practice the presently claimed subject matter of preventing or preventing the progression of Parkinson's disease by administering the claimed compound N-phenyl-7-(hydroxylimino)cyclo-propa[b]chromen-1a-carboxamide without undue experimentation because the artisan would not accept on its face that prevention or prevention of the progression of Parkinson's disease could actually be achieved given the state of the art at the time of the invention.

Based upon the state of the art, as discussed below, and the evidence presented by Applicant, the artisan would have only accepted that the condition could be treated with the compound as instantly claimed.

As set forth in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains the teachings of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112, *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support;* assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added)

The present claims circumscribe the use of the presently claimed compound for the prevention or the prevention of the progression of Parkinson's disease. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering the presently claimed compound that Parkinson's disease would actually be prevented from developing (particularly in patients who are not exhibiting any signs or symptoms of the disease) or worsening or progressing or that the onset of Parkinson's disease could be prevented. In other words, the skilled artisan would have understood the term "prevention" to mean that the claimed compound was capable of impeding the development or progression of such a condition such that it would be "prevented", i.e., reasonably expected not to occur or worsen, in such a population treated via the instantly claimed compound. Because such preventive success is not reasonably possible with most diseases or disorders, especially a condition as complex and poorly understood as Parkinson's disease, the specification, which lacks any direction or guidance as to how prevention or prevention of the progression of Parkinson's disease could actually be achieved, is viewed as lacking an enabling disclosure of the entire scope of the claimed

invention.

Regarding the prevention of Parkinson's disease, the objective truth that such patients may be effectively identified is doubted because, while the state of the art with regard to the identification of patients suffering from or exhibiting symptoms of Parkinson's disease is relatively well developed, the state of the art with regard to the identification of patients at risk for the same is grossly underdeveloped.

In this regard, Jenner ("Presymptomatic Detection of Parkinson's Disease, *J Neural Transm Suppl*, 1993; 40:23-26; Abstract Only) is cited. Jenner states that various method of presymptomatic detection of Parkinson's disease have been identified as potentially applicable, such as, e.g., PET scan, electrophysiology, enzyme assays, olfactory function, etc., but none have been rigorously evaluated for their effectiveness. Jenner further teaches that measurement of pHVA levels has been proposed, as well as measurements of mitochondrial complex I activity and brain glutathione levels, for presymptomatic detection of Parkinson's disease, but none have demonstrated any promise as diagnostic tools for this purpose (abstract).

Given the state of the art, which recognized the inability to formulate an art-accepted protocol for identifying patients at risk for Parkinson's disease due to the great variability in pathophysiological manifestations and the unreliability of various methods of detection in conclusively identifying patients at risk for the disease, one of ordinary skill in the art would not accept on its face Applicant's statement that patients at risk for the condition could accurately be identified without placing a burden of undue experimentation upon the skilled artisan to determine how such an objective could actually be achieved. The artisan would have required sufficient direction as to how, at minimum, the population of patients at risk therefor could have been identified such that the skilled artisan would have been imbued with at least a reasonable expectation of success in identifying such patients and actually having a modicum of success in preventing the development of the condition in a patient. Furthermore, such success would not have been reasonably expected in light of what is presently disclosed because the art at the time of the

invention failed to recognize any effective methods of presymptomatic detection of Parkinson's disease and Applicant has failed to provide any guidance as to how such an objective of identifying patients at risk for Parkinson's disease could actually be achieved. Accordingly, the present specification fails to enable the full scope of this invention as it relates to the objective of preventing Parkinson's disease and, thus, fails to rebut the presumption of unpredictability in the art with regard to this same objective.

Regarding the prevention of the progression of Parkinson's disease, the objective truth that Parkinson's disease can be prevented from progressing is doubted because the complexity of the disorder poses a significant challenge to achieving the objective of preventing the progression of the disease. While it may be true that there are effective therapies that reduce or eliminate symptoms available in the art, the art fails to recognize any mode of therapy that is capable of preventing the eventual progression of the disease.

In this regard, Andersen et al. ("The Hunt for a Cure for Parkinson's Disease", *Sci Aging Knowledge Environ*, 2001 Oct 3; 2001(1):re1) is cited. Andersen et al. teaches that, "Several exciting new scientific advances have been made in the past decade toward both understanding the causes of and finding a cure for Parkinson's disease. Heartened by an acceleration in research findings in the past several years, the government has recently called for an infusion of funds from both the National Institutes of Health and private foundations into this burgeoning area of biomedical research. Most currently available conventional treatments for the disease only temporarily delay symptom presentation while doing nothing to halt disease progression." (abstract) Andersen et al. further states that, "Unfortunately, most current therapies for PD, while often drastically halting or suppressing the symptoms at early stages in the disease, do nothing to prevent disease progression. The most common treatment for the disease is oral administration of the dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA). L-DOPA acts to up-regulate the production of dopamine in the remaining cells in the SN, but does nothing to prevent the eventual death of these cells." (col.2, p.1, para.2)

Given that the art expressly acknowledges that the halting or prevention of the progression of the disease has not yet been an outcome possible to achieve, the skilled artisan would have recognized that the state of the art with regard to such an objective is not well defined, and is, therefore, unpredictable, such that one of ordinary skill in the art would not accept on its face Applicant's statement that Parkinson's disease could be prevented from progressing because the pathophysiology of such a condition is particularly complicated and, as of the time of the invention, such an objective had been impossible to achieve. In light of such, the artisan would have required sufficient direction as to how the administration of the presently claimed compound could actually prevent the progression of disease without requiring an undue level of experimentation such that the artisan would have been imbued with at least a reasonable expectation of success. Such success would not have been reasonably expected given that the prevention of the progression of the disease is not an outcome reasonably expected by one of ordinary skill in the art and, further, Applicant has failed to provide any guidance to this effect. Absent this disclosure, the present specification fails to enable the full scope of this invention as it related to the objective of preventing the progression of the disease and, thus, fails to rebut the presumption of unpredictability in the art with regard to this same objective.

It is in this regard that Applicant is directed to the MPEP at §2164.08. All questions of enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involved the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation.

Applicant provides various examples testing the activity of the instantly claimed compound N-

phenyl-7-(hydroxylimino)cyclo-propa[b]chromen-1a-carboxamide on glutamate receptors and the activity of the same compound to reverse motor deficits in a reserpine-induced akinesia rodent model of Parkinson's disease, demonstrating further that activation of mGluR4 receptors is an effective approach for the treatment of movement disorders, including Parkinson's disease. Please see, e.g., p.14-18 of the instant specification. However, none of these studies demonstrates the ability of the claimed compound to effectively prevent or prevent the progression of Parkinson's disease *per se*. While a lack of a working embodiment cannot be the sole factor in determining enablement, the absence of substantial evidence commensurate in scope with the presently claimed subject matter, in light of the unpredictable nature of the art and the direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole. The instant specification conspicuously lacks any disclosure or teaching of manner and process of using the presently claimed compound for achieving the objective of prevention or prevention of the progression of Parkinson's disease itself. Nowhere does the specification disclose the manner or procedure of using the presently claimed compound N-phenyl-7-(hydroxylimino)cyclo-propa[b]chromen-1a-carboxamide for preventing Parkinson's disease or preventing the progression of Parkinson's disease such that the skilled artisan would have been imbued with at least a reasonable expectation of success in achieving such objective(s) without the burden of an undue level of experimentation.

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the pharmaceutical and chemical arts that experimentation in this particular art is not at all uncommon, but that the level of experimentation required in order to practice this aspect of the invention in the absence of any enabling direction by Applicant would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added)

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the objective of preventing or preventing the progression of Parkinson's disease in a subject using the claimed compound N-phenyl-7-(hydroxylimino)cyclo-propa[b]chromen-1a-carboxamide, could be achieved. In order to actually achieve such a result, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the presently claimed invention.

Conclusion

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Please reference the publication to Marino et al. ("Allosteric Modulation of Group III Metabotropic Glutamate Receptor 4: A Potential Approach to Parkinson's Disease Treatment", *Proceedings of the National Academy of Sciences of the United States of America*, 2003; 100(23):13668-13673).

Rejection of claims 1, 3, 10 and 14 is proper.

Claims 6-7, 11-12 and 15-18 are **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

January 28, 2009

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614